SCIENTIFIC RESEARCH ARTICLE

Preoperative Physical Inactivity Affects the Postoperative Course of Surgical Patients with Lung Cancer

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ABSTRACT. Objective: Preoperative performance status is an important factor in thoracic surgery, but little is known about the effect of preoperative physical activity (PA) on the postoperative course. This study investigated the associations between preoperative PA and postoperative complications and clinical outcomes of lung cancer surgery. **Methods:** This prospective observational study included patients who underwent surgery for lung cancer at a single institution. PA was measured before hospitalization for 5 consecutive days and then after surgery until hospital discharge. The daily step count and time spent performing moderate intensity activity (> 3 metabolic equivalents) were measured with an accelerometer. We examined the correlations between PA and preoperative pulmonary function and physical fitness, and examined the relationship between postoperative complication and PA. Finally, a multivariate analysis was performed with pre-hospital PA as the dependent variable. **Results:** Forty-two patients were analyzed. Univariate analysis found no correlation between pre-hospital PA and preoperative pulmonary function, but found significant positive correlations between pre-hospital PA and time spent performing moderate intensity activity, in-hospital PA, preoperative 6-minute walk distance, and maximum gait speed (r > 0.5, p < 0.01). The nine patients who developed postoperative complications had significantly lower pre-hospital and postoperative step count than the patients with no complication (p = 0.04). Multiple regression analysis showed that pre-hospital PA was significantly associated with time spent performing moderate intensity activity, maximum gait speed, and postoperative complication. **Conclusions:** Evaluation of pre-hospital PA is useful in predicting the postoperative course after lung cancer surgery.

Key words: Lung cancer, Surgical treatment, Preoperative physical activity, Postoperative complication, Accelerometer

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Performance status (PS) is an important prognostic factor for lung cancer and a clinical indicator for surgical treatment [1-3]. Eastern Cooperative Oncology Group / World Health Organization PS is an indicator of general health and activity status on a scale of 0 to 4 [4]. The lower the PS, the higher the activity, which is associated with the survival rate of non-small-cell lung cancer patients [4]. However, the PS is a simple measurement and does not fully reflect the activity level of each individual. A previous study found that physical activity (PA), mainly based on the average number of steps per day, is a strong prognostic factor in the outcome of chronic obstructive pulmonary disease [5]. Lung cancer is the leading cause of cancer death in Japan and is strongly associated with smoking [6]. The data of the cancer registry of Japan showed that the incidence of lung cancer is increasing [7], and surgical treatment is becoming increasingly frequent [8]. Perioperative pulmonary physical therapy for patients with lung cancer is a promising strategy to optimize physical fitness, and may yield improved outcomes such as reduced length of stay or fewer postoperative complications [9,10]. Although several studies have assessed in-hospital PA and postoperative complications in patients with lung cancer [11,12], no study has evaluated the relationship between pre-hospital PA (activity at home) and the postop-

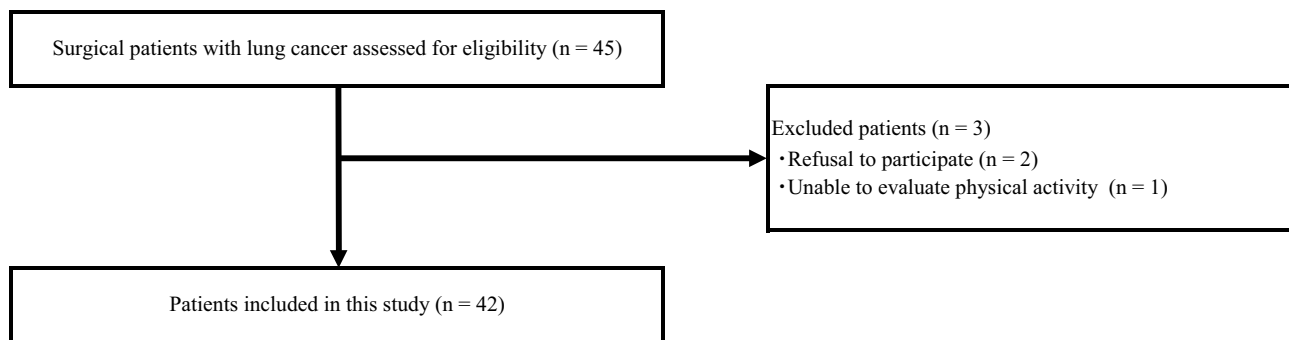**Fig. 1** Flowchart of patient inclusion and exclusion.

erative course. The aim of this study was to examine the relationship between PA and physical function and postoperative complications and to identify the clinical variables related to pre-hospital PA in surgical patients with lung cancer.

Methods

Study design and subjects

This prospective study was conducted from September 2016 to April 2017 in a single institution in Japan. The study was approved by the Human Research Ethics Review Committees of Showa General Hospital (approval number REC-112), and all patients provided informed consent for study participation. All surgical patients were assessed for physical and pulmonary function prior to surgery. Eligible patients had a diagnosis of lung cancer (non-small cell lung cancer), were aged > 18 years, and were scheduled for lung resection. Exclusion criteria were comorbid conditions affecting exercise performance (specifically, musculoskeletal or neurological impairment and cardiac disease) or refusal to participate. During the recruitment period, 45 individuals underwent surgery; however, data from three patients were not included (two who did not provide consent and one whose physical activity was not evaluated) (Fig. 1). Postoperative complications were defined as any postoperative event such as prolonged mechanical ventilation > 48 hours, atelectasis, bacterial pneumonia, cardiac arrhythmia, delirium or prolonged air leak requiring > 5 days of chest tube drainage (Clavien-Dindo grade $\leq$ IVa)[13]. PS was evaluated during the preoperative physical therapy. As a measure of overall health status, the attending anesthesiologist determined the American Society of Anesthesiologists physical status for each patient prior to surgery[14].

Physical function measures

The peripheral muscle strength was assessed on the basis of the quadriceps force (QF), defined as the peak force during maximal isometric knee extension measured using a hand-held dynamometer (μ-TusF-1; Anima Corporation, Tokyo, Japan). The QF of the dominant side was tested in the sitting position with the hip and knee joint flexed at approximately 90°. The highest value of three satisfactory measurements was recorded. The QF was expressed as a percentage of body weight. Grip strength (kg) was measured with a hand dynamometer (T. K. K. 5401; Takei Scientific Instruments Corporation, Niigata, Japan). Measurements were made on the dominant side and the highest value of three technically correct attempts was used in the analysis.

The 6-minute walk test was performed in accordance with published guidelines[15] and the 6-minute walk distance (6MWD) was calculated. Mobility was evaluated using the perceived maximal (fastest) walking speed over 10 meters measured with a stopwatch, with the fastest of two measurements used in the analysis (m/seconds). The maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) were measured as indicators of respiratory muscle strength using a respiratory dynamometer (MicroRPM, Micro Medical/CareFusion, Kent, UK) following the method recommended by the American Thoracic Society/European Respiratory Society[16]. For the MIP measurement, the patient was asked to exhale as much as possible (to residual volume) and then inhale maximally for more than 1 second against the resistance. For the MEP measurement, the patient was asked to inhale as much as possible and then exhale maximally for more than 1 second against the resistance. The measurements were repeated at least three times, and the highest measurements for both MIP and MEP were used in the analysis. Preoperative physical functional assessment was performed 1-2 days prior to surgery, while postoperative assessments were performed as needed with the removal of devices.

Physical activity

PA was determined with an accelerometer (Lifecorder EX, Suzuken Co. Ltd., Nagoya, Japan), which collected data during waking hours in 2-minute epochs. The mean step count and time spent engaged in PA (minutes per day) were evaluated. PA was classified as moderate to vigorous intensity activity (> 3 metabolic equivalents (METs)). We used a PA analysis software package (Liferiser 05 Coach,

Suzuken Co. Ltd.) and Microsoft Excel (Microsoft Corp., Redmond, WA, USA) to analyze the activities measured via the accelerometer[17,18]. Preoperative PA was assessed on 5 consecutive weekdays before hospitalization, while in-hospital PA was assessed during the last 5-7 days of hospitalization. On each assessment day, PA was recorded for at least 8 hours from the time of waking, on the basis of methods used in previous studies[19-21].

Physical therapy

As part of standard perioperative care, all patients received an in-hospital physical therapy consultation 1-2 days prior to surgery. Patients were encouraged to meet the rigorous postoperative early mobilization recommendations for the prevention of postoperative complications and were given instructions on deep breathing and coughing exercises for airway clearance. Postoperative management comprised thoracic drains (all patients were managed with a water seal on the day after surgery), epidural catheters, urethral catheters, oxygen therapy, and intravenous drips. The thoracic tube was removed as early as possible on the basis of the absence of air leaks and drainage status assessed with daily chest x-rays and physical examinations performed by the attending medical doctor. In accordance with the American Thoracic Society/European Respiratory Society guidelines, the attending physical therapist instructed all patients to begin ambulating (i.e., leave their bed) from the day after surgery, if possible[22]. Patients were instructed to at least sit in a chair for 30 minutes and walk 30-50 meters on postoperative day 1. From postoperative day 2 onwards, patients who were able to walk on their own were encouraged to leave the bed as often as possible outside of rehabilitation. In addition, under the supervision of a physical therapist who monitored the pain severity and vital signs, each patient performed 20-40 minutes/day of resistance training and bicycling until discharge from the hospital. During hospitalization, no intervention was implemented on the basis of the activity recorded with the accelerometer.

Statistical methods

Data were expressed as means with standard deviation or medians with interquartile ranges for continuous variables, and as counts with percentages for categorical variables. The Shapiro-Wilk test was used to examine the distribution of the data. The relationship between variables was examined using Pearson's or Spearman's correlation coefficients in accordance with the distribution of the data. Multiple regression analysis was performed to determine the variables associated with the preoperative PA, after correcting for risk factors that were shown to be significant at $p < 0.05$ on univariate analysis. Stepwise multiple regression analysis was undertaken to identify whether the pulmonary function, physical function, step count, total duration of moderate to vigorous activity (> 3 METs) preopera-

tively, and presence of postoperative complications were dependent variables. A p value < 0.05 was considered significant. Analyses were performed using a statistical software package (IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA)).

Results

Patient characteristics

Characteristics of the 42 candidates for lung resection are summarized in Table 1. The PS was 0 and 1 for about 90% of the participants, and the preoperative activity based on the American Society of Anesthesiologists physical status was ≤ 2 in about 90% of patients. All patients were scheduled to undergo video-assisted thoracoscopic surgery or open surgery and had relatively good preoperative respiratory function. Nine patients developed postoperative complications. No patients had more than one complication. All patients were ambulating with or without a gait aid in the intensive care unit as early as the first postoperative day and were discharged from the intensive care unit on postoperative day 2 or 3. All patients had an uneventful postoperative course and were discharged home.

Clinical characteristics of patients with versus without postoperative complications

The group of patients with postoperative complications was significantly older than the group without complications. There were no significant differences between the two groups regarding the history of smoking or alcohol consumption, preoperative pulmonary function, or surgical outcome. The group with postoperative complications had significantly lower preoperative exercise capacity (6MWD) and in-hospital step count than the group without complications (data not shown). Patients with postoperative complications also had a significantly lower pre-hospital step count than those without complications (Fig. 2).

Relationships between clinical variables and pre-hospital PA

Preoperative pulmonary function was only weakly related to participation in daily pre-hospital PA (Table 2). The variables significantly related to pre-hospital PA were preoperative physical function and exercise capacity, step count during the hospitalization period, and duration of activity time before hospitalization.

Factors related to pre-hospital PA in surgical patients with lung cancer

The following variables with significant results in the univariate correlation analyses were entered into the multivariate model: age, sex, preoperative pulmonary function, physical fitness, 6MWD, pre-hospital activity level (daily minutes of activity > 3 METs), and the absence of postop-

Table 1. Characteristics of the 42 patients who underwent lung resection

Age	68.9 ± 10.1
Male, sex	31 (74)
BMI (kg/m^2)	22.7 ± 2.9
Smoking status	
Current or former smoker	34 (81)
Non-smoker	8 (19)
Alcohol history, yes	14 (33)
Underlying disease	25 (59)
Hypertension	17 (40)
Diabetes mellitus	6 (14)
Hyperlipidemia	6 (14)
Bronchial asthma	3 (7)
Preoperative pulmonary function tests	
VC (L)	3.3 ± 0.8
VC % predicted	106 ± 19.5
FEV$_1$ (L)	2.3 ± 0.6
FEV$_1$ % predicted	105 ± 25.2
Performance status (< 1)	38 (90)
ASA-PS (< 2)	36 (86)
Preoperative variables	
Grip strength (kg)	27.6 ± 7.8
QF (kgf/body weight)	0.49 ± 0.1
MIP (cmH$_2$O)	57.7 ± 22.1
MEP (cmH$_2$O)	59.8 ± 20.0
6MWD (m)	481.4 ± 98.4
Maximum gait speed (m/s)	1.7 ± 0.3
Physical activity	
Pre-hospital step count	5093.5 (2542.3 - 8613.3)
In-hospital step count	2410.5 (1652.8 - 3604.3)
Pre-hospital activity level (> 3METs, min)	57.1 (12.8 - 129.5)
Operative modes	
Wedge resection	7
Segmentectomy + wedge resection	10
Lobectomy	18
Lobectomy + lobectomy	4
Pneumonectomy	3
Operation time (min)	134.0 ± 62.3
Intraoperative bleeding loss (ml)	20.0 (10 - 47.3)
Postoperative events	9 (21%)
Prolonged mechanical ventilation (> 48 h)	-
Atelectasis	-
Pneumonia	1
Arrhythmia	3
Delirium	3
Prolonged air leak (> 5 days)	2
Length of stay (days)	9.5 ± 3.6

Data are reported as mean ± standard deviation, n (%), and median (interquartile range). BMI: body mass index; FEV$_1$: forced expired at one second; VC: vital capacity; ASA-PS: American Society of Anesthesiologists physical status; QF: quadriceps force; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; 6MWD: 6-minute walk distance; METs: metabolic equivalents.
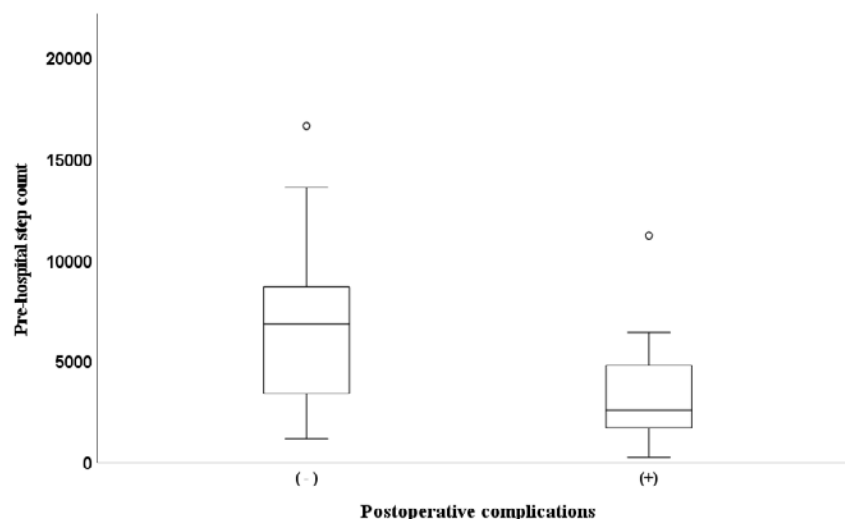
Fig. 2 Comparison of the preoperative physical activity level (step count) of patients with (+) versus without (-) postoperative complications. Data are reported as median (interquartile range) and evaluated using the Mann–Whitney U test. The preoperative step count was significantly lower in the group with postoperative complications than in the group without complications ($p < 0.05$).

Table 2. Univariate correlations between pre-hospital step count and other variables

	Effect size (r)	p value
Age	-0.46	< 0.01
BMI (kg/m^2)	0.12	0.46
Preoperative pulmonary function tests		
FEV$_1$ (L)	0.15	0.36
FEV$_1$ % predicted	-0.26	0.1
VC (L)	0.21	0.2
VC % predicted	0.001	0.9
Length of stay (days)	-0.17	0.27
Preoperative variables		
Grip strength (kg)	0.36	< 0.05
QF (kgf/body weight)	0.44	< 0.01
MIP (cmH$_2$O)	0.3	0.61
MEP (cmH$_2$O)	0.35	< 0.05
6MWD (m)	0.62	< 0.001
Maximum gait speed (m/s)	0.55	< 0.001
Physical activity		
In-hospital step count	0.65	< 0.001
Pre-hospital activity level (>3METs, min)	0.9	< 0.001

BMI: body mass index; FEV$_1$: forced expiratory volume at 1 second; VC: vital capacity; QF: quadriceps force; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; 6MWD: 6-minute walk distance; METs: metabolic equivalents.

erative complications.

Multivariate regression analysis revealed a significant positive relationship between pre-hospital step count and pre-hospital activity level (daily duration of activity > 3 METs) ($p < 0.001$), between pre-hospital step count and preoperative maximum gait speed ($p < 0.001$), and between pre-hospital step count and the absence of postoperative complications ($p = 0.03$); these three variables explained 92% of the variance (Table 3).

Table 3. Clinical variables correlated with pre-hospital step count in multivariate regression analysis

Predictor	Pre-hospital step count		
	β	p value	R^2 (%)
Intercept			92
Duration of pre-hospital activity > 3 METs (min)	0.83	< 0.001	
Maximum gait speed (m/s)	0.27	< 0.001	
Postoperative complication (+)	-0.11	0.03	

ANOVA $p < 0.01$, β: regression coefficient, METs: metabolic equivalents.

Discussion

This study demonstrated that patients with lung cancer with postoperative complications had significantly lower preoperative PA levels than those without postoperative complications, and that preoperative PA was more strongly related to preoperative physical function than to preoperative pulmonary function.

A previous study reported that the duration of hospitalization after lung cancer surgery is increased in patients with lower levels of postoperative PA[11]. This is consistent with our finding that the postoperative PA was significantly lower in the group with postoperative complications than in the group without complications. However, all patients in the present series had an uneventful postoperative course and were discharged home, which was likely related to the efficacy of perioperative physical therapy. Marike et al. showed that the amount of activity during hospitalization is strongly associated with physical function at discharge in patients who have undergone lung cancer resection[23]. Our findings suggest that increasing the PA not only during but even before hospitalization may contribute to the improvement of physical function and the prevention of postoperative complications related to physical inactivity (such as atelectasis and delirium).

Many studies have investigated the association between preoperative pulmonary function and postoperative complications and outcomes[24-26]. Patients with low pulmonary function are at higher risk of postoperative complications and have a poorer prognosis. All patients in our study had relatively good pulmonary function, which suggests that the postoperative complications were related to other factors. Exercise capacity assessment is as essential as pulmonary function testing in predicting postoperative complications after lung resection[27,28]. In our study, there was a significant association between the preoperative 6MWD and postoperative complications. We suggest that patients with relatively good preoperative pulmonary function should undergo multifaceted evaluation, including physical fitness assessment. Furthermore, we consider it extremely important to assess the at-home physical function and PA levels of patients whose lung function is borderline for surgical treatment.

Several reports have studied the relationship between postoperative complications after lung resection and respiratory muscle strength[29,30]. In the present study, the presence of complications was not associated with respiratory muscle strength but was moderately associated with preoperative PA. Future research is needed to determine whether respiratory muscle training is related to improved general activity levels.

In our survey, the factors significantly related to the pre-hospital PA were the 10 meters maximum walking speed, a high pre-hospital activity level (daily duration of activity > 3 METs), and the presence of postoperative complications. Izawa et al. reported an association between 10 meters maximum walking speed and hospital PA in older patients with coronary artery disease[19], which suggests the importance of physical therapy intervention to improve exercise function. Another important finding of our study was that pre-hospital PA was associated with the time spent performing moderate to vigorous intensity activity (> 3 METs) before surgery. The preoperative activity level (> 2 METs) of lung transplant recipients is reportedly lower than that of healthy subjects, and does not return to the level of healthy subjects after surgery[2].

Our findings suggest that walking speed and exercise intensity are also involved in the overall activity level of patients with lung cancer. Recent studies have demonstrated the importance of PA in patients with lung cancer[1,2], and of cooperating with local governments to encourage improvement in PA[2]. Additionally, low activity and depression are associated in patients with lung cancer[31], and PA assessment is an important indicator in postoperative follow-up[32].

Recently, telemedicine (telehealth) with a smartphone and an accelerometer has been increasingly used for perioperative patients with lung cancer; however, it is difficult to conduct telemedicine follow-up for patients with low activity[32]. In Japan, it is important to provide comprehensive physical therapy for low-activity patients not only in the acute phase, but also while in hospital and in the community to improve their activity levels.

Some limitations of the current study should be ac-

knowledged. First, relatively few subjects were recruited because the study was conducted in a single center that only performs a limited number of surgical procedures for lung cancer annually. Second, this study included subjects with relatively good preoperative respiratory function and there was no standardization of treatment, such as the inclusion of only patients with anatomical lung resections. Finally, the preoperative activity assessment did not cover all yearly seasons. Future multicenter studies with larger cohorts that include patients with impaired pulmonary function are needed to determine how preoperative PA affects the outcomes of lung cancer surgery.

Conclusions

The present study demonstrated that assessing preoperative PA may be useful in predicting postoperative complications in patients with lung cancer. Preoperative activity correlates with physical function but not with preoperative pulmonary function. The use of an accelerometer to assess preoperative activity levels may be useful as an indicator to determine the need for preoperative physical therapy to prevent complications.

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